

Ordinary differential equation for local accumulation time

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Cell differentiation in a developing tissue is controlled by the concentration fields of signaling molecules called morphogens. Formation of these concentration fields can be described by the reaction-diffusion mechanism in which locally produced molecules diffuse through the patterned tissue and are degraded. The formation kinetics at a given point of the patterned tissue can be characterized by the local accumulation time, defined in terms of the local relaxation function. Here, we show that this time satisfies an ordinary differential equation. Using this equation one can straightforwardly determine the local accumulation time, i.e., without preliminary calculation of the relaxation function by solving the partial differential equation, as was done in previous studies. We derive this ordinary differential equation together with the accompanying boundary conditions and demonstrate that the earlier obtained results for the local accumulation time can be recovered by solving this equation. [doi:[10.1063/1.3624898](https://doi.org/10.1063/1.3624898)]

I. INTRODUCTION

Cell differentiation in a developing organism is determined by gene expression that is controlled by concentration fields of signaling molecules called morphogens.^{1,2} These concentration fields, called morphogen gradients, can be formed by reaction-diffusion mechanisms. In the simplest case, this mechanism involves local production of the morphogen, its diffusion through the tissue, and degradation (source-sink model).^{3–10} Initially, the morphogen concentration is zero. The concentration increases with time and approaches its position-dependent steady-state value as time goes from zero to infinity. If the gradient formation at a given point of the patterned tissue is fast compared to the cell differentiation at this point, then the latter occurs under the action of the steady-state gradient. When the time scale separation does not exist, the cell differentiation occurs under the action of the morphogen concentration profile that varies in time. Crick¹¹ was the first who understood the role of the time scale separation in the dynamics of cell differentiation controlled by morphogen gradients.

When tackling the question of the time scale separation one faces with a conceptual problem: how to introduce a local time that characterizes the morphogen gradient formation at a given point x of the patterned tissue. In recent papers,^{12,13} we suggested an approach to the problem based on the use of the local relaxation function. We introduced the local accumulation time, $\tau(x)$, defined in terms of this function, that provided a time scale for the gradient formation at point x . For several simple models, we derived expressions that give $\tau(x)$ as a function of the problem parameters such as the diffusion constant of the morphogen and its degradation rate, the distribution of the source of the morphogen, and the length of the interval that models the patterned tissue. In these papers, we also discuss biological applications of the local accumulation time. Recently, Kolomeisky¹⁴ applied our approach to consider the gradient formation prob-

lem in the framework of a discrete model of the morphogen dynamics.

In the present paper, we show that one can find $\tau(x)$ avoiding consideration of the relaxation function. It turns out that $\tau(x)$ satisfies an ordinary differential equation. We derive this equation as well as accompanying boundary conditions and demonstrate how the earlier derived results for $\tau(x)$ can be obtained by solving this equation. The new way of finding $\tau(x)$ allows one to bypass the need of solving the partial differential equation that is necessary for finding the local relaxation function.

The outline of the paper is as follows. In Sec. II, we formulate the generic model and introduce some definitions and relations that are used in Sec. III when deriving the ordinary differential equation for $\tau(x)$. The expressions for $\tau(x)$ obtained for different particular reaction-diffusion models in Refs. 12 and 13 are recovered by solving the ordinary differential equation for $\tau(x)$ in Sec. IV. Some concluding remarks are made in final Sec. V.

II. MODEL AND DEFINITIONS

Consider a one-dimensional model of the patterned tissue, in which the tissue is modeled by an interval of length L with reflecting boundaries. Let $c(x, t)$ be the particle concentration at point x of the interval, $0 < x < L$, at time t . The particles are injected into the interval with the position-dependent injection rate $q(x)$, which is independent of time. The source of the particles is characterized by the total injection rate, $Q = \int_0^L q(x)dx$, and the injection density, $p_q(x) = q(x)/Q$, that is normalized to unity. Injection starts at $t = 0$, when the interval is free from particles. The particles diffuse with diffusivity D and are degraded with the rate constant k .

As $t \rightarrow \infty$, $c(x, t)$ approaches its steady-state (ss) value $c_{ss}(x)$. It is convenient to describe the time course of the concentration at point x in terms of the local relaxation

function $R(t|x)$:

$$\begin{aligned} c(x, t) &= c_{ss}(x) + [c(x, 0) - c_{ss}(x)]R(t|x) \\ &= c_{ss}(x)[1 - R(t|x)], \end{aligned} \quad (2.1)$$

where we have used the fact that $c(x, 0) = 0$ in the second equality. The notation $R(t|x)$ is used to stress the point that our analysis focuses on time-dependent formation of the concentration profile at a fixed point x . The relaxation function,

$$R(t|x) = 1 - \frac{c(x, t)}{c_{ss}(x)}, \quad (2.2)$$

monotonically decreases from unity at $t = 0$ to zero as $t \rightarrow \infty$.

The local accumulation time, $\tau(x)$, is defined in terms of the relaxation function as^{12,13}

$$\tau(x) = \int_0^\infty R(t|x)dt. \quad (2.3)$$

It provides a time scale that characterizes the gradient formation at point x . Denoting the Laplace transform of a function $f(t)$ by $\hat{f}(s)$: $\hat{f}(s) = \int_0^\infty e^{-st} f(t)dt$, we can write $\tau(x)$ as

$$\tau(x) = \hat{R}(0|x) = \lim_{s \rightarrow 0} \left(\frac{1}{s} - \frac{\hat{c}(x, s)}{c_{ss}(x)} \right). \quad (2.4)$$

We assume that the relaxation function tends to zero as $t \rightarrow \infty$ fast enough, so that the integral in Eq. (2.3) converges, and the limit in Eq. (2.4) is well defined.

The concentration $c(x, t)$ can be expressed in terms of the propagator or the Green's function, $G(x, t - t_0|x_0)$, which is the probability density of finding the particle at point x at time t on condition that the particle was injected at point x_0 at time t_0 . The expression is

$$c(x, t) = \int_0^t dt_0 \int_0^L G(x, t - t_0|x_0)q(x_0)dx_0. \quad (2.5)$$

Introducing the notation $\langle G(x, t|x_0) \rangle_q$ for the propagator averaged over x_0 ,

$$\langle G(x, t|x_0) \rangle_q = \int_0^L G(x, t|x_0)p_q(x_0)dx_0, \quad (2.6)$$

we can write Eq. (2.5) as

$$c(x, t) = Q \int_0^t \langle G(x, t - t_0|x_0) \rangle_q dt_0. \quad (2.7)$$

Using the relation $c_{ss}(x) = Q \langle \hat{G}(x, 0|x_0) \rangle_q$, we can express $\tau(x)$, Eq. (2.4), in terms of the Laplace transform of the averaged propagator:

$$\tau(x) = \lim_{s \rightarrow 0} \frac{1}{s} \left[1 - \frac{\langle \hat{G}(x, s|x_0) \rangle_q}{\langle \hat{G}(x, 0|x_0) \rangle_q} \right]. \quad (2.8)$$

Taking the limit we obtain

$$\tau(x) = - \frac{1}{\langle \hat{G}(x, 0|x_0) \rangle_q} \frac{\partial \langle \hat{G}(x, s|x_0) \rangle_q}{\partial s} \bigg|_{s=0}. \quad (2.9)$$

In Sec. III, we use this relation to derive an ordinary differential equation for $\tau(x)$.

III. THEORY

The local accumulation time, Eq. (2.9), can be written as the ratio of functions $\mu(x)$ and $\nu(x)$,

$$\tau(x) = \frac{\mu(x)}{\nu(x)}, \quad (3.1)$$

defined as

$$\mu(x) = \langle w(x|x_0) \rangle_q, \quad \nu(x) = \langle u(x|x_0) \rangle_q, \quad (3.2)$$

where

$$u(x|x_0) = \hat{G}(x, 0|x_0) = \int_0^\infty G(x, t|x_0)dt, \quad (3.3)$$

$$w(x|x_0) = - \frac{\partial \hat{G}(x, s|x_0)}{\partial s} \bigg|_{s=0} = \int_0^\infty t G(x, t|x_0)dt. \quad (3.4)$$

Note that function, $u(x|x_0)$, has the following interpretation: $u(x|x_0)dx = \hat{G}(x, 0|x_0)dx$ is the mean occupation time^{15,16} of the interval of length dx located at point x by a diffusing particle that starts from point x_0 . We present some arguments that, hopefully, make this interpretation intuitively appealing in the Appendix.

The propagator, $G(x, t|x_0)$, satisfies

$$\begin{aligned} \frac{\partial G(x, t|x_0)}{\partial t} &= D \frac{\partial^2 G(x, t|x_0)}{\partial x^2} \\ &\quad - kG(x, t|x_0), \quad 0 < x, x_0 < L, \end{aligned} \quad (3.5)$$

with the initial and boundary conditions

$$G(x, 0|x_0) = \delta(x - x_0), \quad \frac{\partial G(x, t|x_0)}{\partial x} \bigg|_{x=0, L} = 0. \quad (3.6)$$

Integrating Eq. (3.5) with respect to time from zero to infinity we find that function $u(x|x_0)$ satisfies

$$D \frac{d^2 u(x|x_0)}{dx^2} - ku(x|x_0) = -\delta(x - x_0), \quad 0 < x, x_0 < L, \quad (3.7)$$

where we have used the initial condition in Eq. (3.6). Multiplying both sides of Eq. (3.5) by t and then integrating with respect to time from zero to infinity, we find that function $w(x|x_0)$ satisfies

$$D \frac{d^2 w(x|x_0)}{dx^2} - kw(x|x_0) = -u(x|x_0), \quad 0 < x, x_0 < L, \quad (3.8)$$

where we have used the definition of function $u(x|x_0)$, Eq. (3.3).

Similar manipulations with the boundary conditions in Eq. (3.6) lead to the following boundary conditions for Eqs. (3.7) and (3.8):

$$\frac{du(x|x_0)}{dx} \bigg|_{x=0, L} = \frac{dw(x|x_0)}{dx} \bigg|_{x=0, L} = 0. \quad (3.9)$$

Solving Eq. (3.7) with the boundary conditions in Eq. (3.9), we obtain

$$u(x|x_0) = \frac{\lambda}{D \sinh(L/\lambda)} \times \begin{cases} \cosh\left(\frac{L-x_0}{\lambda}\right) \cosh\left(\frac{x}{\lambda}\right), & 0 < x < x_0 \\ \cosh\left(\frac{x_0}{\lambda}\right) \cosh\left(\frac{L-x}{\lambda}\right), & x_0 < x < L \end{cases}, \quad (3.10)$$

where $\lambda = \sqrt{D/k}$.

Averaging Eqs. (3.7)–(3.9) over x_0 , we find that the functions $v(x)$ and $\mu(x)$ satisfy

$$D \frac{d^2 v(x)}{dx^2} - k v(x) = -p_q(x), \quad 0 < x < L, \quad (3.11)$$

$$D \frac{d^2 \mu(x)}{dx^2} - k \mu(x) = -v(x), \quad 0 < x < L, \quad (3.12)$$

with boundary conditions

$$\left. \frac{dv(x)}{dx} \right|_{x=0,L} = \left. \frac{d\mu(x)}{dx} \right|_{x=0,L} = 0. \quad (3.13)$$

To derive the desired ordinary differential equation for $\tau(x)$, we write Eq. (3.1) as

$$v(x)\tau(x) = \mu(x). \quad (3.14)$$

Differentiating this twice with respect to x , we obtain

$$v(x) \frac{d^2 \tau(x)}{dx^2} + 2 \frac{dv(x)}{dx} \frac{d\tau(x)}{dx} + \tau(x) \frac{d^2 v(x)}{dx^2} = \frac{d^2 \mu(x)}{dx^2}. \quad (3.15)$$

Using the relation

$$\frac{d^2 \mu(x)}{dx^2} - \tau(x) \frac{d^2 v(x)}{dx^2} = \frac{1}{D} (p_q(x)\tau(x) - v(x)), \quad 0 < x < L, \quad (3.16)$$

that follows from Eqs. (3.11), (3.12) and (3.14), we can write Eq. (3.15) as

$$D v(x) \frac{d^2 \tau(x)}{dx^2} + 2D \frac{dv(x)}{dx} \frac{d\tau(x)}{dx} - p_q(x)\tau(x) = -v(x), \quad 0 < x < L. \quad (3.17)$$

This is the desired ordinary differential equation for the local accumulation time.

Boundary conditions for this equation can be obtained from Eqs. (3.13) and (3.14). They have the following form:

$$d\tau(x)/dx|_{x=0,L} = 0. \quad (3.18)$$

An expression giving function $v(x)$ in terms of the injection density, $p_q(x)$, can be obtained by averaging $u(x|x_0)$,

Eq. (3.10), over x_0 . The result is

$$v(x) = \frac{\lambda}{D \sinh(L/\lambda)} \left[\cosh\left(\frac{L-x}{\lambda}\right) \times \int_0^x \cosh\left(\frac{x_0}{\lambda}\right) p_q(x_0) dx_0 + \cosh\left(\frac{x}{\lambda}\right) \int_x^L \cosh\left(\frac{L-x_0}{\lambda}\right) p_q(x_0) dx_0 \right]. \quad (3.19)$$

Relations in Eqs. (3.17)–(3.19) are the main results of the present paper. In Sec. IV, we use them to derive the expressions for the local accumulation time obtained earlier by means of the local relaxation function.^{12,13}

IV. ILLUSTRATIVE EXAMPLES

We begin with the case of the source localized at the left boundary of the interval,

$$p_q(x_0) = \delta(x_0). \quad (4.1)$$

In this case function $v(x)$, Eq. (3.19), takes the form

$$v(x) = \frac{\lambda \cosh((L-x)/\lambda)}{D \sinh(L/\lambda)}, \quad 0 < x < L, \quad (4.2)$$

and Eq. (3.17) can be written as

$$\frac{d^2 \tau(x)}{dx^2} - \frac{2}{\lambda} \tanh\left(\frac{L-x}{\lambda}\right) \frac{d\tau(x)}{dx} - \frac{1}{\lambda} \tanh\left(\frac{L}{\lambda}\right) \delta(x)\tau(x) = -\frac{1}{D}, \quad 0 < x < L. \quad (4.3)$$

Boundary conditions for this equation are given in Eq. (3.18).

Integrating Eq. (4.3) over a small interval near $x = 0$, it can be shown that $\tau(x)$ satisfies

$$\frac{d^2 \tau(x)}{dx^2} - \frac{2}{\lambda} \tanh\left(\frac{L-x}{\lambda}\right) \frac{d\tau(x)}{dx} = -\frac{1}{D}, \quad 0 < x < L, \quad (4.4)$$

with boundary conditions

$$\left. \frac{d\tau(x)}{dx} \right|_{x=0} = \frac{1}{\lambda} \tanh\left(\frac{L}{\lambda}\right) \tau(0), \quad \left. \frac{d\tau(x)}{dx} \right|_{x=L} = 0. \quad (4.5)$$

Solving the equation we find

$$\tau(x) = \frac{1}{2k} \left[1 + \frac{L}{\lambda} \coth\left(\frac{L}{\lambda}\right) - \frac{L-x}{\lambda} \times \tanh\left(\frac{L-x}{\lambda}\right) \right], \quad 0 < x < L, \quad (4.6)$$

where we have used the relation $k = D/\lambda^2$.

As the length of the interval tends to infinity, $L \rightarrow \infty$, the formulas significantly simplify. In this case

function $v(x)$ is

$$v(x) = \frac{\lambda}{D} e^{-x/\lambda}, \quad x > 0, \quad (4.7)$$

and the differential equation for $\tau(x)$ takes the form

$$\frac{d^2\tau(x)}{dx^2} - \frac{2}{\lambda} \frac{d\tau(x)}{dx} = -\frac{1}{D}, \quad x > 0. \quad (4.8)$$

This equation should be solved with the boundary condition

$$\left. \frac{d\tau(x)}{dx} \right|_{x=0} = \frac{1}{\lambda} \tau(0). \quad (4.9)$$

The solution is given by

$$\tau(x) = \frac{1}{2k} \left(1 + \frac{x}{\lambda} \right), \quad x > 0. \quad (4.10)$$

Next, we consider the case of distributed source of the particles injected into a semi-infinite interval, $L \rightarrow \infty$,

$$p_q(x_0) = \frac{1}{l_q} e^{-x_0/l_q}, \quad x_0 > 0, \quad (4.11)$$

where l_q is the mean injection length, $l_q = \int_0^\infty x_0 p_q(x_0) dx_0$. Here, function $v(x)$, Eq. (3.19), is

$$v(x) = \frac{1}{k(\lambda^2 - l_q^2)} (\lambda e^{-x/\lambda} - l_q e^{-x/l_q}), \quad x > 0, \quad (4.12)$$

and Eq. (3.17) leads to

$$\begin{aligned} \frac{d^2\tau(x)}{dx^2} - 2 \frac{e^{-x/\lambda} - e^{-x/l_q}}{\lambda e^{-x/\lambda} - l_q e^{-x/l_q}} \frac{d\tau(x)}{dx} \\ + \frac{(\lambda^{-2} - l_q^{-2}) l_q e^{-x/l_q}}{\lambda e^{-x/\lambda} - l_q e^{-x/l_q}} \tau(x) = -\frac{1}{D}, \quad x > 0. \end{aligned} \quad (4.13)$$

This equation should be solved with the reflecting boundary condition at $x = 0$,

$$\left. \frac{d\tau(x)}{dx} \right|_{x=0} = 0. \quad (4.14)$$

One can check that the solution is given by

$$\begin{aligned} \tau(x) = \frac{1}{2k} \left[\left(1 + \frac{x}{\lambda} \right) \frac{\lambda e^{-x/\lambda}}{\lambda e^{-x/\lambda} - l_q e^{-x/l_q}} \right. \\ \left. + \frac{2l_q^2}{l_q^2 - \lambda^2} \right], \quad x > 0. \end{aligned} \quad (4.15)$$

As the mean injection length vanishes, $l_q \rightarrow 0$, this reduces to the expression for $\tau(x)$ in Eq. (4.10), as it must be.

The expression for $\tau(x)$ given in Eqs. (4.6), (4.10) and (4.15) has been derived earlier^{12,13} using the relaxation function. Here, we have demonstrated that these results can be obtained by solving the ordinary differential equation for the local accumulation time. One can find detailed discussion of $\tau(x)$ for the three models considered above, including plots of

the x -dependences of the local accumulation time in Ref. 13. In these three models one can obtain analytical expressions for $\tau(x)$ by both methods, since the injection rates, $q(x)$, are simple functions of x . When $q(x)$ is not that simple, to find $\tau(x)$, one has to numerically solve the problem. Here, the suggested approach has an obvious advantage since it allows one to avoid the numerical solution of the partial differential equation and find $\tau(x)$ by solving the ordinary differential equation, Eq. (3.17).

V. CONCLUDING REMARKS

In Refs. 12 and 13, we study the local accumulation time, $\tau(x)$, using a straightforward approach, i.e., we first find the local relaxation function, which is then used to find $\tau(x)$. Here we suggest an alternative way of finding $\tau(x)$, which avoids the calculation of the relaxation function. Equations (3.17)–(3.19) show that $\tau(x)$ can be found by solving the ordinary differential equation. This is the main result of the present paper.

One can write Eq. (3.17) in a form that is identical to the equation for the mean first-passage time¹⁷

$$\begin{aligned} D \left[\frac{d^2\tau(x)}{dx^2} - \beta \frac{dU(x)}{dx} \frac{d\tau(x)}{dx} \right] \\ - \gamma(x) \tau(x) = -1, \quad 0 < x < L, \end{aligned} \quad (5.1)$$

where $\beta U(x) = -\ln(v(x)^2)$ and $\gamma(x) = p_q(x)/v(x)$ can be interpreted as a potential at point x measured in the thermal energy units and a position-dependent sink term, respectively. However, the local accumulation time, which describes the formation of nonequilibrium steady-state concentration profile, is a fundamentally different quantity than the mean first-passage time. The latter characterizes an individual particle, whereas the former characterizes collective behavior of the system. When the interval is not free from particles at $t = 0$, the local accumulation time becomes a functional of the initial concentration profile, $c(x, 0)$, and the theory developed above is inapplicable.

Finally, we note that the definition of $\tau(x)$ in Eq. (2.3) is based on the interpretation of the negative partial derivative of the local relaxation function with respect to time as the probability density, $\varphi(t|x)$, of time associated with the formation of the steady-state concentration profile at point x ,

$$\varphi(t|x) = -\frac{\partial R(t|x)}{\partial t}. \quad (5.2)$$

The mean time that characterizes the formation process, $\tau(x)$, is

$$\tau(x) = \int_0^\infty t \varphi(t|x) dt. \quad (5.3)$$

Integrating this by parts, one recovers the definition of $\tau(x)$ in Eq. (2.3).

At the same time, using Eqs. (3.1)–(3.4) one can write $\tau(x)$ as

$$\tau(x) = \frac{1}{\langle \hat{G}(x, 0|x_0) \rangle_q} \int_0^\infty t \langle G(x, t|x_0) \rangle_q dt. \quad (5.4)$$

A comparison of the expressions in Eqs. (5.3) and (5.4) shows that the probability density $\varphi(t|x)$ can be written in terms of the propagator averaged over the particle injection point x_0 as

$$\varphi(t|x) = \frac{\langle G(x, t|x_0) \rangle_q}{\langle \hat{G}(x, 0|x_0) \rangle_q}. \quad (5.5)$$

This expression allows the following interpretation: The probability density is the ratio of the probability of finding a particle, injected at $t = 0$, within the interval dx located at point x at time t , $\langle G(x, t|x_0) \rangle_q dx$, to the mean occupation time of this interval, $\langle \hat{G}(x, 0|x_0) \rangle_q dx$, discussed in the Appendix.

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APPENDIX: MEAN OCCUPATION TIME

Let $\{x(t')\}_t$ be a particle trajectory observed for time t , and $I_\Delta(x)$ be the indicator function of interval Δ defined as

$$I_\Delta(x) = \begin{cases} 1, & x \in \Delta \\ 0, & x \notin \Delta \end{cases}. \quad (A1)$$

Time $\theta_\Delta(\{x(t')\}_t)$ spent by the trajectory within the interval, called the occupation time,^{15,16} is the functional of the trajectory of the form

$$\theta_\Delta(\{x(t')\}_t) = \int_0^t I_\Delta(x(t')) dt'. \quad (A2)$$

The mean occupation time spent within the interval by trajectories that start from point x_0 , $\langle \theta_\Delta(\{x(t')\}_t) \rangle_{x_0}$, is given by

$$\langle \theta_\Delta(\{x(t')\}_t) \rangle_{x_0} = \int_0^t \langle I_\Delta(x(t')) \rangle_{x_0} dt', \quad (A3)$$

where the double angular brackets with subscript x_0 , $\langle \dots \rangle_{x_0}$, denote the averaging over all possible trajectories starting from x_0 .

The indicator function can be written as an integral of the δ -function over the interval Δ :

$$I_\Delta(x) = \int_\Delta \delta(x' - x) dx'. \quad (A4)$$

Substituting this into Eq. (A3) we obtain

$$\langle \theta_\Delta(\{x(t')\}_t) \rangle_{x_0} = \int_0^t dt' \int_\Delta \langle \delta(x' - x(t')) \rangle_{x_0} dx'. \quad (A5)$$

The integrand here is the path integral representation of the propagator¹⁸

$$\langle \delta(x - x(t)) \rangle_{x_0} = G(x, t|x_0). \quad (A6)$$

Therefore, the mean occupation time is

$$\langle \theta_\Delta(\{x(t')\}_t) \rangle_{x_0} = \int_0^t dt' \int_\Delta G(x', t'|x_0) dx'. \quad (A7)$$

As the observation time tends to infinity, $t \rightarrow \infty$, the mean occupation time in Eq. (A7) takes the form

$$\langle \theta_\Delta(\{x(t')\}_\infty) \rangle_{x_0} = \int_\Delta \hat{G}(x, 0|x_0) dx. \quad (A8)$$

This shows that $\hat{G}(x, 0|x_0) dx$ is the mean occupation time of the interval of length dx located at point x by trajectories which start from x_0 .

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